REMARKS

Withdrawal of Finality

Applicants respectfully request that the finality of the Office Action be withdrawn in view of new rejections. For instance, claims 93 and 121 are newly rejected under 35 U.S.C. 112, second paragraph. This rejection was not necessitated by Applicants' prior amendments. Similarly, claim 19 is newly rejected under 35 U.S.C. 102(b) over Balazs and Turley. These rejections were not necessitated by Applicants' prior amendments.

Status of the Claims

Claims 2, 3, 6-9, 11-14, 19, 22-27, 30-38, 41, 42, 46-54, 59, 60, 63-67, 69-70 and 72-124 are pending in the present application.

Rejection of Claims 122 and 123 Under 35 U.S.C. 112, First Paragraph

Claims 122 and 123 are rejected by the Examiner under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

""0.0001 mg to 100 mg"

The Examiner maintains that the recitation requiring 0.0001 mg to 100 mg is considered new matter." Again, Applicants disagree. It should be noted that the portion of the specification referred to by the Examiner at page 5 of the Office Action has been misinterpreted by the Examiner. The Examiner's interpretation is clear error as the specification does not limit the invention in the manner suggested by the Examiner. Accordingly, the rejection of claims 122

and 123 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement should be withdrawn by the Examiner.

Rejection of Claims 93 and 121 Under 35 U.S.C. 112

Claims 93 and 121 are rejected by the Examiner under 35 U.S.C. 112, second paragraph, as being indefinite. This new rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Claims 93 and 121 are said to be indefinite because of the phrase "low purity." Although Applicants do not agree that this phrase is indefinite, this phrase has been deleted from claim 93. This amendment is clearly a non-narrowing claim amendment. Claim 121 does not contain the language referred to by the Examiner. Clarification is requested. Accordingly, the rejection under 35 USC 112, second paragraph, should be withdrawn by the Examiner.

Claim Rejections - 35 U.S.C. §102

Balazs

Claims 19 (newly rejected), 23, 42, 50, 51, 59, 66, 70, 72-76, 78, 80, 81, 91-95, 112, and 117-121 are rejected by the Examiner under 35 U.S.C. 102(b) as being anticipated by U.S. Patent 4,303,676 to Balazs for the reasons set forth on pages 7-9 of the Office Action.

Balazs Does Not Teach The Claimed Purity

In order to clarify the present invention, each of the independent claims has been amended to recite that the complex carbohydrate contains up to 5% by weight protein contaminants. See page 13, lines 31-33 of the specification. In this regard, Applicants respectfully submit that the Examiner has misinterpreted the Balazs statement "...and containing

about 1% sodium hyaluronate and 0.5 to 1.5% protein" to be the same as that claimed by the present invention. Indeed, as Balazs recites in claim 1 thereof, the 0.5 to 1.5% protein is in relation to the amount of 1% sodium hyaluronate.

> 1. A water based, viscoelastic composition comprising, by weight, (a) mixture of different sodium hyaluronate fractions, a first such fraction having a molecular weight of about 10,000 to 200,000 and a second fraction having a molecular weight of about 1 x 10^6 to 4.5 x 10^6, the ratio of said fractions being in the range of about 0.3-2.1, (b) about 50 to 400% of protein based on the weight of ingredient (a), said protein being derived from the natural material from which the hyaluronate is obtained, and (c) the balance being water. (emphasis added)

Claim 1 clearly indicates that the percentages are by weight and that the 50 to 400% protein is based on the weight of ingredient (a), which is hyaluronic acid. Therefore, if the Balazs composition was a solution/suspension containing 1% by weight sodium hyaluronate, then it would contain from 0.5% to 4.0% by weight protein based on sodium hyaluronate. The description cited by the Examiner at page 6, first paragraph of the Office Action more accurately relates to a solution containing 1% sodium hyaluronate and from 0.5 to 1.5% protein based on the amount of sodium hyaluronate, OR 50% to 150% protein based on the concentration of hyaluronic acid. Such high protein contaminant levels are acceptable for cosmetic preparations but not for orally ingestable products. The Balazs patent is clearly directed to cosmetic compositions as is stated in the Abstract and the Summary of the Invention. The detailed description refers only to application to the skin. The oral toxicity test was not required because such testing is not required for products applied to the skin, which is the intended use of the Balazs composition. The skin test and the eye test (dropping into the conjuctiva of the eye, not the Owl Monkey Eye Test) are required since cosmetics are applied to the skin and can potentially get into the eye.

In contrast, the claimed invention recites a complex carbohydrate such as sodium hyaluronate that contains up to 5% protein relative to the 100% complex carbohydrate. Therefore, a solution containing 1% sodium hyaluronate would contain maximally 0.05% protein.

In summary, the complex carbohydrates of the claimed invention are purer than the sodium hyaluronate described and claimed by Balazs. The Balazs HPE mixture is very crude compared to the present invention and clearly does not anticipate (or suggest) the present invention.

Not only are the complex carbohydrates of the present invention purer (containing significantly less protein as compared to the concentration of the Balazs complex carbohydrate,) but as a result the complex carbohydrates of the present invention are clear and transparent. In contrast, Balazs states that the HPE is "a white to yellow, non-transparent...." It is obvious from the description and claims of the Balazs patent that the HPE (sodium hyaluronate) is crude and highly impure as compared with that described and claimed in the present invention. Even so, the complex carbohydrates of the present invention will not pass the owl monkey eye test.

The Examiner's comments with respect to claim 72 [and claim 50] in the second full paragraph on page 6 of the Office Action are clearly inaccurate since the Examiner has misinterpreted the impurity levels between the present invention and Balazs.

The Examiner Concedes that Balazs Does Not Describe Oral Administration or Nutritional Value

A Liquid Substance Is Not Necessarily Safe For Oral Use By Humans Or Other Animals

The Examiner indicates that because the Balazs preparation, HPE, is in liquid form it "clearly can be administered orally, and therefore can be considered a food or drink or nutrient".

This conclusion is clearly factually incorrect. Indeed, if this were a correct statement, logic would follow that such liquid forms as gasoline, sodium hydroxide, hydrochloric acid, and numerous other liquids could clearly be administered orally. Further, following the Examiner's logic, such harmful liquids could be considered a food or drink or nutrient. This reasoning is patently false. Simply because a composition is a liquid does not mean that it is safe for oral consumption. It would, however, be acceptable for cosmetic use, which is the full intent of Balazs.

A Substance That Is A Sterile Liquid Is Not Necessarily Safe For Human Consumption

The Examiner states that "HPE is a "sterile liquid" and "One can drink a sterile liquid". Again, the Examiner's analysis is clearly wrong and obviously greatly generalizing. Indeed, sterile liquids may contain toxic chemicals. Therefore, such sterile liquids can be harmful and detrimental and even cause death. For instance, gasoline, sodium hydroxide, hydrochloric acid and many other toxic liquids are sterile. However, if one tries to drink such sterile liquids, serious illness and most likely death will result.

The Examiner should further note that there is nothing in the Balazs specification that indicates that the HPE has been filter sterilized. Therefore, the method of sterilizing the Balazs liquid HPE must involve addition of some chemical. The example provided is propyl p-hydroxybenzoate (propylparaben) at 0.12 g/100 ml. According to the "Handbook of Pharmaceutical Excipients", Third Edition, Propylparaben is only soluble in water at a concentration of 1g/2500 ml. This translates to 0.12g/300 ml. Therefore, the example would contain a suspension of propyl p-hydroxybenzoate (propylparaben). This is not acceptable for an oral solution. Also, according to the same reference, propylparaben (propyl p-hydroxybenzoate)

is a good preservative for mold and yeast but not for bacteria, especially Gram negative bacteria. Therefore, this preservative would not be expected to sterilize a crude preparation extracted from rooster combs.

The Balazs Preparation of HA Contains Chemicals Of High Oral Toxicity

The Balazs specification recites the following:

> "To obtain HPE, a batch of rooster combs is homogenized, minced or simply cut into small sections after being thoroughly washed with water. The washed and homogenized rooster combs are then extracted with water under constant stirring. The weight ratio of combs to water is typically about 1:4, that is, about 3.75 liters of water for every kilogram of combs, although this ratio may, of course, vary. The extracting solution should also have bacteriostatic agents added thereto. Examples of such bacteriostatic agents include chloroform, cetylpyridinium chloride and propylparaben. After the extraction procedure is completed, the tissue (combs) is separated from the fluid, for example, by filtration, centrifugation or decantation. The extract contains, inter alia, Na--HA and various proteins. The extract is then precipitated using ethanol or acetone and the like; or it can be lyophilized."

Applicants submit the following analysis based on this description:

First, the process for preparation of HPE is extremely crude, which explains why the protein content is so high (50% to 400% of the hyaluronic acid content, per Balazs Claim 1).

Second, the chemicals used for extraction are all toxic substances (see the attachments to this Reply) and include chloroform, cetylpyrimidium chloride, acetone and ethanol. The Balazs description does not recite the use of absolute ethanol, so one skilled in the art would expect that the ethanol would be denatured and thus toxic to mammals. Even though Balazs states that these chemicals are removed, there is nothing in the description that teaches how they could be removed. Removal of such chemicals is not readily understood in this art. The description of Balazs clearly does not fully teach the Balazs invention (as modified by the Examiner) and to the

extent that the Examiner's improper interpretation is accurate, the Balazs description is non-enabling with respect to the Examiner's position.

Third, the methods described in Balazs (e.g. filtration, centrifugation or decantation and lyophilization) will not remove the above-identified chemicals from a preparation. Therefore, the statement that :

> "HPE is prepared from the skin of animals which have been slaughtered for human consumption. During the purification procedure no toxic chemicals are used, and all other chemicals which are used during this process are removed. Therefore oral toxicity studies are deemed not to be necessary"

provides no evidence that the HPE is safe when administered orally.

Moreover, the statement that no toxic chemicals are used in the purification procedure is clearly untrue. As demonstrated by the attachments to this Reply and as well known to one of ordinary skill in the art, chemicals such as chloroform, cetylpyridinium chloride, ethanol and acetone are all toxic chemicals. Balazs simply provides no description as to how these chemicals are removed.

Fourth, Balazs also states that all other chemicals which are used during this process are removed. As indicated earlier, the procedure described for preparation of HPE does not provide methods for removal of any of the chemicals used. Therefore, one cannot assume that this HPE would be safe for oral administration.

Fifth, the HPE is also described as "... a white to yellow, non-transparent sterile liquid solution..." It is unclear on what basis Balazs or the Examiner believes that the solution is sterile. It is impossible that such a crude liquid that is white to yellow and non-transparent would be sterilized by filter sterilization as this requires passage through less than a 0.4 micron filter. Such a process would remove all particles, including bacteria. Such a treatment would

produce a transparent sterile liquid. Therefore, the Balazs method of providing a "sterile" solution must involve addition of bacteriostatic chemicals (e.g. propylparaben.) The amount of propylparaben used in the example (0.12 g/100 mL) is suspect as this amount of propylparaben is not soluble in water (see attached technical article.). Clearly, either the Examiner is misinterpreting the Balazs reference or this reference is non-enabling with the respect to the Examiner's argument.

Sixth, as discussed above, the complex carbohydrates of the claimed invention are purer than the sodium hyaluronate described and claimed by Balazs. The Balazs HPE mixture is very crude compared to the present invention. Not only do the claimed complex carbohydrates contain significantly less protein as compared to the concentration of the Balazs white to yellow, non-transparent complex carbohydrate, but the complex carbohydrates of the present invention are clear and transparent. Even so, the complex carbohydrates of the present invention will not pass the owl monkey eye test.

Although Balazs states that the HPE solution need not be tested for oral toxicity, this conclusion does not mean that it is safe since the unsupported conclusion does not withstand technical analysis.

As for the Examiner's position that if it exists it may be a food or drink, such an interpretation is not consistent with any description of Balasz. In this regard, Applicants' arguments of record are herein incorporated by reference.

Pharmacologically Effective

Balasz does not teach a pharmacologically effective composition, that is, one having an amount of ingredient hyaluronic acid that is provides a treatment effect as claimed herein. The Examiner has no legal basis for rendering Applicants' claimed term virtually meaningless.

Accordingly, reconsideration and withdrawal of the rejection of the claims over the Balazs reference are respectfully requested.

Turley

Claims 19 (newly rejected), 22, 23, 42, 50, 51, 59, 66, 70, 72-76, 78, 80, 81, 91-95, 112, and 117-121 and 124 are rejected by the Examiner under 35 U.S.C. 102(b) as being anticipated by WO 97/25051 to Turley. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The Examiner Misinterprets the Molecular Weight Limitation vis-à-vis Turley

The Examiner states that:

> The molecular weight of the hyaluronic acid can range from 30,000 to 2,000,000 Daltons, thereby encompassing all of the molecular weight fractions recited in the rejected claims.

The Examiner's technical analysis is factually in error and confuses the protein and dextran standards. It is well known in the art that 30,000 to 2,000,000 Daltons using the dextran standard of Turley is well below the 1,000,000 dalton limitation using the protein standard. For instance, 2,000,000 Daltons using the dextran standard is about 650,000 Daltons using the protein standard. See page 25 of Turley.

The Examiner's attention is also directed to the attached Rule 132 Declaration. More specifically, for the research leading to the present application and at the time that the present application was prepared, Applicants based the molecular weight measurements on the protein standard rather than the dextran standard. The specific method used was size exclusion chromatography (gel permeation chromatography or HPLC) and the protein standards were Immunoglobulin M, with a molecular weight of 900,000 daltons, Thyroglobulin with a molecular weight of 670,000 daltons, Gamma globulin with a molecular weight of 158,000 daltons and Ovalbumin with a molecular weight of 44,000 daltons. Using this method, one of the complex carbohydrates used by applicants as an example of an effective high molecular weight component was confirmed to have a molecular weight greater than 1,000,000 daltons by a third party laboratory, using the same protein standards (see attached document titled "Certificate of Analysis No. 030791).

Accordingly, Turley does not teach or suggest the present invention.

Claim Rejections - 35 U.S.C. §103

Claims 2, 6, 7, 11, 12, 14, 19, 22, 23, 36, 37, 41, 42, 46-51, 53, 54, 59, 66, 69, 70, 72-95, 112-115, 117 and 118-121 are rejected by the Examiner under 35 U.S.C. 103(a) as being obvious over U.S. Patent 4,303,676 to Balazs.

This rejection is traversed for the reasons stated above and for the reasons of record. Thus, this rejection should be withdrawn.

Rejection of Claims Over WO 97/25051 to Turley et al. Under 35 U.S.C. 103; Rejection of Claims Over WO 97/25051 to Turley et al. in View of WO 92/22585 to Gallina Under 35 U.S.C. 103

Claims 2, 6, 7, 11, 12, 14, 19, 22, 23, 36, 37, 41, 42, 46-51, 53, 54, 59, 66, 69, 70, 72-95, 112-115, 117 and 118-121 are rejected by the Examiner under 35 U.S.C. 103 over WO 97/25051 to Turley et al. Claims 2, 6, 7, 11, 12, 14, 19, 22, 23, 36, 37, 41, 42, 46-51, 53, 54, 59, 66, 69, 70, 72-95, 112-115, 117 and 118-121 are rejected by the Examiner under 35 U.S.C. 103 over WO 97/25051 to Turley et al. in view of WO 92/22585 to Gallina. These rejections are respectfully traversed. Reconsideration and withdrawal thereof are requested.

The Examiner's technical analysis is factually in error and confuses the protein and dextran standards. It is well known in the art that 30,000 to 2,000,000 Daltons using the dextran standard of Turley is well below the 1,000,000 dalton limitation using the protein standard. For instance, 2,000,000 Daltons using the dextran standard is about 650,000 Daltons using the protein standard. See page 25 of Turley.

Indeed, Turley et al. teaches away from the present invention when she clearly states that a molecular weight >1,000,000 daltons will not be orally effective (see page 12, lines 8-14). In fact, Turley et al. teach away from using any composition with a molecular weight >1,000,000 daltons. In the present invention, one of the molecular weight fractions recited by the amended claims is >1,000,000 daltons.

The Examiner's reliance upon the Gallina reference does not correct this deficiency. Thus, the present invention is not obvious over Turley et al. optionally in view of Gallina.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Marc S. Weiner (Reg. No. 32,181) at the telephone number of (703) 205-8000, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

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Respectfully submitted,

By_____

Marc S. Weiner
Registration No.: 32,181
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road
Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000
Attorney for Applicant